REMARKS

In order to expedite prosecution, claims 19-26 have been canceled, thus obviating the 112, 2nd paragraph rejection as well as the two Section 102 rejections.

Claim 27 is amended to recite "recombinant" as supported on at least page 4, line 1; "Fab' fragment" with support found on at least page 7, line 5; and "at least about 95%" as supported on, *e.g.*, page 22, lines 22-23. Claims 30-31 are added herein which find support on at least page 22, lines 17-23; page 7, lines 4-5; and page 23, lines 1-2. In that the amendments do not introduce new matter, entry thereof is respectfully requested.

While claim 29 has been withdrawn from consideration, Applicants note that this is due to a species election. Applicants will demonstrate herein that the generic claims are patentable, and therefore request consideration of species claim 29 which depends on the generic claim.

The volume number for the Inouye *et al. Protein Engineering* reference is added responsive to item 4 on page 2 of the Office Action. Reconsideration of the objection to the specification is respectfully requested.

Claims 19-20 and 23-28 are rejected under the judicially created doctrine of obviousness-type double patenting (OTDP) as being unpatentable over claims 1, and 3-10 of US Patent No. 6,066,719 (hereinafter "the '719 patent").

Applicants note for the record that the claims of the '719 patent don't require a correctly disulfide linked antibody fragment wherein the purity of the correctly disulfide linked antibody fragment in a composition thereof is at least about 95%. Moreover, Applicants note that while the claims of the '719 patent are directed to an antibody which comprises a linear VH-CH1-VH-CH1 heavy chain fragment associated with two light chains, the claims herein concern a genus of antibody fragments, of which

a linear $F(ab')_2$ fragment is, but one, example.

Notwithstanding the above and without acquiescing in the merits of the rejection, Applicants submit herewith a terminal disclaimer over the '719 patent. Reconsideration and withdrawal of the OTDP rejection is respectfully requested.

The Examiner urges that claims 19-20 and 23-28 are directed to an invention not patentably distinct from claims 1, 3-10 of the '719 patent.

Without acquiescing in the merits of the rejection, Applicants submit herewith an assignment (Reel 7796, Frame 0660) which relates to both the '719 patent as well as the present application, and demonstrates that the invention of the '719 patent and that of the present application (which is a continuation of USSN 09/249,230, which is a divisional of the application that issued as the '719 patent) were commonly owned (by Genentech) at the time the invention in the present application was made, thus precluding a rejection under 35 USC Section 103(a) based on the commonly assigned case as a reference under 35 USC Section 102(f), (g) or (e) for the present application.

Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 19-28 are rejected under 35 USC Section 103(a) as being unpatentable over Carter *et al.* (US Patent No. 6,054,297) or Hudziak *et al.* (WO89/06692) and further in view of Morimoto *et al. J. Biochem. Biophys. Methods* 24:107-17 (1992).

The Examiner urges that Morimoto *et al.* teach a $F(ab')_2$ fragment of an antibody that is purified to greater than 98% and the antibody fragment is eluted with PBS.

Applicants submit that the presently claimed invention is patentable over the cited art.

Claim 27 herein concerns a composition comprising a recombinant correctly disulfide linked antibody fragment, wherein the purity of the correctly disulfide linked antibody fragment in the composition is at least about 95%.

As explained in the paragraph bridging pages 3-4 of the application, the present application identifies a problem associated with the formation of recombinant immunoglobulins; recombinant production of antibody fragments results in the formation of functional $F(ab')_2$ antibodies as well as a variety of incorrectly associated light and heavy fragments. The most difficult impurity to remove was found to be an antibody fragment whose light and heavy chains fail to associate through disulfide bonding (an "incorrectly disulfide linked antibody fragment"). The low pH hydrophobic interaction chromatography (LPHIC) method described in the present application provides one means for substantially removing this contaminant.

The correctly and incorrectly disulfide linked antibody fragments are characterized in the paragraph bridging pages 31-32 and in Figs. 3A-3D. There, the specification explains that the incorrectly disulfide linked antibody denatured into light and heavy chain molecules at pH 3.2, whereas correctly disulfide linked antibody denatured at pH 2.5. Fig. 4, discussed on page 32, lines 11-13, demonstrates that at higher pHs (*e.g.* pH 6.5) the % light chain (representing incorrectly disulfide linked antibody fragment contamination) was greater. Using LPHIC, the amount of the incorrectly disulfide linked antibody fragment contaminant could be reduced such that the purity of the correctly disulfide linked antibody fragment was about 95% or more.

Morimoto *et al.* fails to discuss the problem identified in the present application, *i.e.*, the presence of incorrectly disulfide linked antibody fragments in a preparation of recombinantly produced antibody fragments. Morimoto *et al.* is also deficient in describing a composition wherein such a contaminant has been removed.

The antibody fragments in Morimoto *et al.* weren't recombinantly produced; rather they were obtained by pepsin digestion of intact mouse mAbs (page 108). According to Morimoto *et al.*, the antibodies were eluted from the HIC column at pH 7.4 (page 110, first paragraph). Hence, at the pH's recommended by Morimoto *et al.* the amount of incorrectly disulfide linked antibody fragment contamination would have exceeded that specified by the present claims. This is illustrated with reference to Fig. 4 of the present application; the extent of contaminating incorrectly disulfide linked antibody fragment in a preparation generated according to Morimoto's teachings would be greater than that seen at pH 6.5, since such contamination increases with increasing pH.

Hence, Applicants submit that the presently claimed invention is patentable over the cited art. Reconsideration and withdrawal of the rejection is respectfully requested.

Applicants believe that this application is now in condition for allowance and look forward to early notification to that effect. However, if there are outstanding issues to be resolved, Applicants invite the Examiner to call the undersigned to address those and thereby expedite prosecution.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please replace the paragraph on page 1, line 11 with the following:

This is a continuation of Serial No. 09/249,230 filed on February 11, 1999 **(now U.S. patent no. 6,214,984)**, which is a divisional application of Serial No. 08/811,757 filed on March 6, 1997 (now U.S. patent no. 6,066,719), which is a continuation of 08/425,763 filed April 20, 1995[;], (now U.S. patent no. 5,641,870), which applications are incorporated herein by reference and to which [application(s)] **applications** priority is claimed under 35 USC §120.

Please replace the paragraph starting on page 2, line 16 with the following:

HIC has also been used for purifying antibody fragments. Inouye *et al.*, Protein Engineering, **[pgs 6, 8 and] 6(8):**1018-1019 (1993); Inouye *et al.*, Animal Cell Technology: Basic & Applied Aspects 5:609-616(1993); Inouye *et al.*, Journal of Biochemical and Biophysical Methods 26:27-39 (1993); and Morimoto *et al.*, Journal of Biochemical and Biophysical Methods 24:107-117 (1992) prepared $F(ab')_2$ fragments from pepsin digests of mouse IgM monoclonal antibodies using a TSKgel Ether-5PW™ HIC column. The antibody fragments were salted out with 60% ammonium sulfate and the precipitates were dissolved into phosphate-buffered saline (PBS, pH 7.4) containing 1M ammonium sulfate. This solution was loaded onto the HIC column which had been equilibrated with PBS also containing 1M ammonium sulfate. The $F(ab')_2$ fragments which were adsorbed onto the column were eluted by reducing the ammonium sulfate concentration in the elution buffer to 0M. Inouye *et al.* found that the fraction containing the $F(ab')_2$ was homogeneous by both SDS-PAGE and gel filtration HPLC. The method was considered to be suitable for large-scale purification of $F(ab')_2$ fragments. Similarly, Rea *et al.*, Journal of Cell. Biochem. Suppl. 0, Abstract No. X1-206 (17 Part A), p.50 (1993) evaluated HIC for purification of a $F(ab')_2$ fragment produced by peptic digestion of a murine IgG_{2b} monoclonal antibody. Protein A purification for removal of residual intact antibody preceded the HIC step. The purification

performance of three different HIC columns was tested at several different salts and pHs. POROS PE™ (Phenyl ether) was found to be the best column and phosphate-buffered sodium sulfate at pH 8 gave the best resolution of the $F(ab')_2$ fragment.

IN THE CLAIMS:

Please amend the following claim:

27. (Amended) A composition comprising a physiologically acceptable carrier, and a **recombinant** correctly disulfide linked antibody fragment selected from the group consisting of a $F(ab')_2$ fragment, Fab fragment, **Fab' fragment** and linear $F(ab')_2$ fragment, wherein the purity of the correctly disulfide linked antibody fragment in the composition is **[more than] at least** about **95** **[98]**%.

Please cancel claims 19-26 without prejudice or disclaimer.

Please add the following claims:

30. (New) A composition comprising a mixture of incorrectly disulfide linked antibody fragment and correctly disulfide linked antibody fragment, wherein the purity of the correctly disulfide linked antibody fragment in the composition is at least about 95%, and wherein the antibody fragment is selected from the group consisting of a $F(ab')_2$ fragment, Fab fragment, Fab' fragment and linear $F(ab')_2$ fragment.

31. (New) The composition of claim 30 further comprising a physiologically acceptable carrier.